A REPORT

UPON THE

BIOLOGY OF SYPHILIS.

BY

J. E. R. McDONAGH, F.R.C.S.,

SURGEON TO OUT-PATIENTS, LONDON LOCK HOSPITAL.

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A REPORT UPON THE BIOLOGY OF SYPHILIS.

It is proposed in the present report to set out a statement of the tests employed in the detection of syphilis, and of the fallacies connected with the use of those tests; the statement being based on the original investigations of the author into the application of those tests, and into the life-history of the specific organism to which syphilis is due. As many of the arguments used in this report depend upon the acceptance of the life-cycle of the organism of syphilis, to which I have given the name of *Leucocytozoon syphilidis*, instead of the more commonly accepted name *Spirochæta pallida*, it is necessary for me, first of all, to summarise this life-cycle as described more fully by me in previous articles (1, 2).

The Cause.

The cause of syphilis is, in my opinion, a small body which consists almost entirely of nuclein, to which the name of spore may be given. As this small body has to give rise to several others, each much larger than itself, it is obliged to enter a cell, which happens to be, in the case of syphilis, a connective tissue cell.

From the protoplasm of the connective tissue cell, the spore builds up an elaborate lipoid-protein complex, which forms a colloidal membrane in which the body, or, as it is now called, the trophozoite, develops.

In this envelope the nucleus either buds to form sexual merozoites, or it divides and subdivides to form an asexual spore cyst. The former course occurs in every case of syphilis, while the latter, up till now, has only been found in the lymphatic glands from severe cases of early generalised syphilis. An asexual spore cyst may bud to form daughter spore cysts, by which time the parasite has become extracellular, owing to the degeneration of both the protoplasm and the nucleus of the connective tissue cell.

In the other mode of development of the trophozoite, 7–15 bodies are formed, each one presenting a lecithin-globulin envelope of its own, so in the full stage of development no background is seen at all. When fully developed the cell bursts, allowing the sexual merozoites to escape, when they become both male and female gametocytes. One of the points which determine the sex of the merozoites is doubtless the quantity of the lecithin-globulin that each bud takes with it. The male gametocytes are, according to my own observation, optically more active than the female ones. Optical activity is exhibited by most lipoid-proteins, and serves well for picking out the syphilitic bodies in a section.

Both the male and female gametocytes are motile, but not

flagellated; the male consists of three nuclear bodies, while the female contains a nucleus at her upper end and one or two very actively motile blepharoplasts at her lower end. By the time the female has reached the size of a red blood corpuscle she loses her blepharoplasts, becomes stationary, and, in those females which are about to be fertilised, the nucleus comes from the upper pole, takes a central position, and fills up practically the whole cell. The blepharoplasts of protozoa are probably analogous to the nucleoli of nuclei, as in both cases one is dealing with a mass of nuclein in a lipoid-protein envelope.

The male gametocyte, on the other hand, usually enters a large mononuclear leucocyte, wherein the three nuclear bodies increase in size to develop into a coil, and from each nuclear body a number of spirochætæ arise like the spokes of a wheel from its axle. The spirochætæ break loose and each can then be recognised as a true *Spirochæta pallida*. In the extracellular development, each nuclear body divides and subdivides, so that a rosette-like appearance is formed. Several bodies may break away *en masse*, in the shape of a chain, which ultimately breaks up into distinct coccus-like forms, or discrete coccus-like forms may at first break away. Each coccus-like body contains two rods, which give it the appearance of a diplococcus, and these rods develop into thick and unevenly-coiled spirochætæ, which eventually become typical *Spirochætæ pallidæ*.

The intracellular development has been found in every syphilitic lesion so far examined by me, while the extracellular development has been found to occur only in chancres and condylomata, two lesions which are especially rich in spirochætæ. Therefore, provided the circumstances are favourable for the formation of spirochætæ, the male gametocyte will develop extracellularly, by which means more spirochætæ are formed.

The immature spirochæta which is first formed in this extracellular route resembles the *refringens* type; therefore it is very probable that a spirochæta, in two stages of its development, is indistinguishable from the *Spirochæta refringens* and the *Spirochæta pallida*.

In cultures the male gametocyte develops extracellularly.

Fertilisation, again, does not always appear to take place in the same stereotyped manner, as in some cases the spirochæta appears to enter the female nucleus, wherein it becomes lost; or, in other cases, to become connected with the female nucleus by a skein. In both cases, the nucleus, which contains both male and female elements, migrates again to the upper pole; such a cell is a zygote.

In the nine instances in which fertilisation has been studied by me, only one spirochæta has been observed to enter the female, and it takes about an hour to become entirely lost to view. While entering, the whole cell is in active motion, but once the spirochæta has entered, the cell comes to a sudden standstill, and appears to become covered with a mantle. This mantle has strong reducing properties, and is of a lecithin-globulin nature, with an extra supply of fatty acid, as is shown by its marked affinity for methylene red and pyronin. The result is, that in zygotes the lecithin-globulin envelope is much more marked than in the morphologically identical

female gametocytes, and in consequence they are more highly refractile.

A few minutes after impregnation, a polar body is expelled with considerable force from the cell, and again another, after an interval of a minute or two. During the extrusion of the polar bodies the cell is very actively motile, but it becomes stationary immediately after the second has been ejected. The polar bodies contain a lecithin-globulin protoplasm, and also some nuclein.

The nucleus of the zygote divides and subdivides into sporoblasts; the sporoblasts may further divide and subdivide *in situ* to form sporozoites, or a sporoblast may escape and form sporozoites independently.

Certain objections have been raised to the theory which has just been described. It is contended that the *Spirochæta pallida* has been obtained in pure culture, and that animals have been infected with such cultures. I have, however, been able to culture the *Spirochæta pallida* and have shown that it develops extracellularly (2). It is possible to lay too much stress upon cultures, especially in the case of protozoa. With bacteria and fungi, the greatest morphological differences exist between the same organism in the body, and in cultures, not to mention the variations produced by the different media upon which they are grown. The difference is likely to be greater when a highly developed organism like a protozoon is compared growing *in corpore* with its growth *in vitro*.

The statement that animals can be infected with syphilis from cultures of the *Spirochæta pallida* is no objection to my theory, for the following reasons:—

1. In many instances, if a sufficient quantity of a certain organism be injected into an animal, inflammation will result, and some of the organisms may be found in the urine and blood-stream. This is not evidence that the animal is suffering from the specific disease caused by that organism.

It must not be forgotten that, if a sufficient quantity of wax or fat be injected into a rabbit's testicle, fine particles of the same may be found later in the blood-stream and in the urine.

2. Considering the resistance of the spores, and their small size compared with that of the spirochætæ, they can be easily overlooked and injected with the latter, when only spirochætæ were supposed to be present. If looked for in cultures of the *Spirochæta pallida*, these small bodies can always be found. Therefore, what is happening in the test animal's body, may be no more than is taking place in a culture tube.

The other points are, that the phases described and depicted (2) are cell degenerations, nuclear degenerations or "körpereigene" structures. The chemistry of the *Leucocytozoon syphilidis* and the host's protecting cells (3) shows that these views are untenable.

From the above description of the life-history of the organism of syphilis, I think I am justified in assigning it to the order Sporozoa and to the sub-class Telosporidia, since the spores are formed at the end of a cycle. The order is doubtless the Coccidiidea and the species which most befits it is the Leucocytozoon: hence a good name for the syphilitic parasite would be *Leucocytozoon syphilidis*.

The Wassermann's Reaction.

A negative Widal does not invariably mean that a patient is not suffering from enteric fever, and similarly for a negative Wassermann. As a positive Widal proves that the patient has had, or has typhoid, so does a positive Wassermann prove that he has had, or has syphilis.

For all practical purposes the proof of a positive reaction is absolute, for although leprosy, trypanosomiasis and some cases of malaria give a reaction like that of syphilis, their presence in this country is so rare that it is seldom that a difficulty in differential diagnosis arises.

Sporadic cases have been described where a positive Wassermann has been obtained in diseases other than syphilis; in over 15,000 tests I have had 12 such instances. It is very difficult to exclude syphilis, say of some 10, 15, or 20 years' standing, history being untrustworthy. For instance:—

Case 1.—A man was admitted into hospital for pains in the stomach region and vomiting. Diagnosis, malignant disease. Wassermann positive; no history or sign of syphilis. Operation was advised but patient refused. About a year later patient came up to hospital complaining of pains in his legs. Again the reaction was positive. He was found to have Argyll-Robertson pupils and the case was therefore tabes.

Although a positive reaction is a proof of syphilis it must not be forgotten that it may not necessarily mean that the trouble for which the patient seeks advice is syphilitic. Syphilitic patients are by no means immune to tuberculosis, malignant disease, and the various forms of leucæmia, all of which may produce symptoms which are clinically very difficult to distinguish from syphilis.

The many modifications of the reaction which have been made, have increased the incidence of positive reactions in persons who have never had syphilis. The reaction which Wassermann described is laborious, but nevertheless the most trustworthy. Since the reaction is empirical, all attempts should be made to do away with the empiricism, rather than to simplify the technique. Observations are now being carried on by me to elucidate the cause of the reaction, and I hope that ere long it will be practicable to explain the rationale of the reaction, and to substitute a simple scientific reaction in its place.

The interpretation of a positive and negative Wassermann reaction will be as follows, according to the various stages of the disease:—

Primary Stage.—A positive reaction in the case of a doubtful sore is proof of syphilis, and the patient should receive treatment at once. A negative reaction is valueless. Not more than 40 per cent. of cases react positively before any secondary symptoms have appeared.

Secondary Stage.—The interpretation of the result will depend upon whether the patient has been treated or not, and how soon the examination is made after cessation of treatment.

Taking all cases up till the end of the second year, 85 per cent. are positive, *i.e.*, when only mercury has been used.

Cases of secondaries which have not been treated, 97 per cent. are positive. These percentages are taken from my last 5,000 cases.

The occurrence of a negative reaction in 3 per cent. of the cases, is not for the same reason that a negative Widal occurs in the severest forms of enteric fever; on the contrary, the severer the syphilis the stronger is the reaction. The fault lies in an imperfect technique. While inactivating the serum it is not improbable that some of the antibody becomes fixed, since if no heat is used and the serum is kept for at least 48 hours and used active, positive results have been obtained with the same sera which, when inactivated, gave a negative result. The complement in the serum is possibly to blame for this fixation, and this disappears, even when sera are kept at 0° C. for 48 hours. Similar results have been obtained by precipitating all the complement or complementoid bodies before use, by means of barium sulphate.

Latent Stage.—When no symptoms of disease are present, 80 per cent. are positive; the remaining 20 per cent. may be negative, (*a*) because the syphilitic virus has disappeared or is dormant, and there is no specific reacting substance in the serum; (*b*) because the patient is under treatment, or under the influence of recent treatment.

Tertiary Syphilis.—Taking all patients in the tertiary stage, 70 per cent. give a positive result. The reason why so many cases in this stage, even if they exhibit obvious symptoms, are negative has not yet been solved.

Syphilis of the Nervous System.—When cerebral endarteritis occurs early in syphilis, the Wassermann's reaction is positive; when it occurs late in the disease, as a symptom of general arteriosclerosis, the reaction is more often negative than positive.

In cases of syphilitic cerebro-spinal meningitis, the Wassermann's reaction may be either negative or positive.

In tabes 60 per cent., in G.P.I. 100 per cent., give a positive reaction, so long as the condition is active. Many cases of G.P.I. during the period of remission give a negative reaction.

In nervous syphilis, an examination of the cerebro-spinal fluid is more important than one of the blood.

In cases of cerebral endarteritis, whether they occur early or late in the disease, the cerebro-spinal fluid is generally normal.

In cerebro-spinal meningitis, there is always a lymphocytosis, an excess of globulin, and a positive Wassermann's reaction. All three reactions may disappear as a result of treatment, but sooner or later, in the majority of cases, they become positive again.

In tabes and G.P.I., there is always a lymphocytosis, a positive Nonne Apelt's reaction (excess of globulin), and a positive Wassermann's reaction, so long as the condition is active.

In testing for the Wassermann's reaction in the cerebro-spinal fluid, it is always necessary to use the fluid in gradient strengths, as otherwise a negative reaction may be obtained in an undoubted syphilitic affection. As cerebro-spinal fluid has no complement-fixing capacity, even 1,000 per cent. can be used for the Wassermann's reaction, *i.e.*, ten times the usual quantity of fluid undiluted.

Conceptional Syphilis.—When a woman is infected with syphilis at the time of conception, during the child-bearing period the reaction is often negative.

If the syphilis is contracted before she becomes pregnant, or while she is pregnant, the disease runs its usual course, so the Wassermann's reaction is positive.

Congenital Syphilis.—Infants born with symptoms of the disease always give a positive Wassermann's reaction. In cases of syphilis hereditaria tarda, the reaction is also positive.

It is extremely difficult to influence the Wassermann's reaction by treatment; in fact, a positive test may be obtained years after all symptoms have vanished. On the other hand, adults with stigmata of congenital syphilis not infrequently give a negative reaction.

As an aid to diagnosis, Wassermann's reaction may be of some value.

(1) Differential diagnosis between varicose ulcer and gumma may be difficult, and since such ulcers usually occur in women, history throws little light upon the case.

(2) Diagnosis between gummata, tubercle, and new growth of the testes.

(3) Diagnosis between periostitis and sarcoma. Limbs have been been amputated for malignant disease, when a syphilitic periostitis was the cause of the swelling.

(4) Diagnosis between gumma of liver and malignant growth.

(5) Diagnosis between syphilitic disease, tubercle, and carcinoma of rectum.

Because a positive reaction is given, a conclusion must not be hastily drawn that the lesion under question is syphilitic, for it is possible for a man with malignant disease to have had syphilis. Therefore the reaction can only be an adjunct to the clinical diagnosis.

The Wassermann Reaction as Influenced by Treatment.

In the primary stage, when the reaction is negative before treatment with salvarsan is commenced, most cases give a positive reaction after treatment. This is most marked about the 48th hour, but commences to show itself about the 17th hour. In some cases, on the other hand, the reaction does not become positive until the 5th day.

Although it may remain positive for several days, the degree diminishes generally about the 3rd week, till it becomes negative before the 8th. If the reaction is only slightly positive after the injection, it becomes negative much earlier. If the serum is tested in diminishing strengths to estimate its reagin* content, one can estimate how close to the secondary stage the patient is, and, roughly, how many subsequent injections will be necessary to produce a possible cure.

If the first injection gives rise to only a weak reaction, then three or four more will undoubtedly suffice to make the reaction negative; if, however, the reaction is strong, then the patient is in the secondary stage, and will require at least 3 grams of salvarsan or neo-salvarsan, before the desired effect is obtained.

Case 2.—Intra-urethral chancre, 14 days' duration, 6 weeks after intercourse; slight inguinal adenitis; spirochætæ found.

* Since the reacting substance in the Wassermann's reaction is not a true antibody, it has received the name of "reagin."

No. of injection, and result.		24 hours after.	48 hours after.	5th day.	10th day.	14th day.
1st injection... ...	−	++	+++	+++		
2nd injection (8th day after 1st)	+++	+	++			+++
3rd injection (21st day after 2nd)	+++	−	+++	+++		
4th injection (8th day after 3rd)	+++	−	−	−	+	
5th injection (14th day after 4th)	−	−	−	+		
6th injection (8th day after 5th)	+	−	−	−		

The reaction was tested on the 7th, 14th, 21st, and 28th days after the last injection, and was negative on each occasion. Patient was put on mercury for a year, and 6 months afterwards Wassermann's reaction was positive.

CASE 3.—Two chancres on penis, two on scrotum; no adenitis; date of infection not clear; spirochætæ found.

No. of injection, and result.		24 hours after.	48 hours after.	5th day.
1st injection	−	−	+	++
2nd injection (8th day after 1st)	++	−	+	++
3rd injection (8th day after 2nd)	++	−	−	−
4th injection (8th day after 3rd)	−	−	−	−

The reaction was tested on the 7th, 14th, 21st, and 28th days after the last injection, and was negative on each occasion.

The reaction was tested again 1 and 2 years later with negative results.

CASE 4.—Chancre, internal canthus of eye; adenitis, pre-auricular and cervical; date of infection uncertain; spirochætæ found.

No. of injection, and result.		24 hours after.	48 hours after.	5th day.	10th day.	17th day.
1st injection... ...	−	−	+	++		
2nd injection (8th day after 1st)	+++	++	+++	++	+	
3rd injection (17th day after 2nd)	++	++	++	++		
4th injection (8th day after 3rd)	+	−	−	−	−	++
5th injection (21st day after 4th)	−	−	−			

On testing the reaction on the 7th, 14th, 21st, and 28th days after the last injection, it was found to be negative on each occasion. Mercury was given for 1 year, and blood was tested again 6 months and a year later; on the latter occasion it gave a positive result.

In the primary stage, it is necessary to test the blood 48 hours after, and the 5th day after the first injection; and, if positive on either occasion, to repeat the injection on the 8th day. Then it is necessary to test the blood weekly, and repeat the injections until the Wassermann's reaction is negative on the 7th day after the last injection. When this is the case, the patient should only be passed when the blood remains negative, tested weekly, for another month.

Unfortunately, it is rare to get a case so early that the reaction does not become positive as the result of an injection. A few have been seen, but it is thought wiser to give a second injection for safety. In every case mercury should be prescribed, for from 12 to 18 months.

When the reaction becomes strongly positive after an injection, and in cases in which it is markedly positive before treatment is commenced, no further blood tests need be made until before and after the 4th injection, as in my experience, 4 injections are the minimum likely to be required to produce a negative result.

Case 5.—Chancre on penis, general adenitis, and headaches at night-time.

No. of injection, and result.		24 hours after.	48 hours after.	5th day.
1st injection	+++	+++	+++	+++
2nd injection (8th day after 1st)	+++	+	+	++
3rd injection (8th day after 2nd)	+	−	+	−+
4th injection (8th day after 3rd)	−	−	−	−

The reaction was also found to be negative on the 7th, 14th, 21st, and 28th days after the last injection. Mercury was prescribed for 18 months, but 6 months later Wassermann's reaction was positive.

Case 6.—A typical case of early generalised syphilis, rash, sore throat, etc.

No. of injection, and result.		24 hours after.	48 hours after.	5th day.
1st injection	+++	+++	+++	+++
2nd injection (8th day after 1st)	+++	+++	+++	+++
3rd injection (8th day after 2nd)	++	+++	++	+++
4th injection (8th day after 3rd)	+++	+++	+++	+
5th injection (8th day after 4th)	−	+	++	−
6th injection (8th day after 5th)	−	−	−	−
7th injection (8th day after 6th)	−	−	−	−

The reaction was also found to be negative on the 10th, 14th, and 28th days after the last injection. Mercury was taken for 6 months only; 6 months later Wassermann's reaction was negative, but a year later it had become positive again.

In the tertiary stage, the Wassermann reaction behaves much in the same way as it does in the primary and secondary, except for one peculiar phenomenon which is occasionally to be noted, that is, that a case with a strong positive reaction before treatment may become negative immediately after an injection, and remain so from 24 to 72 hours, and then become quite positive again. On repeating the injection, the same thing may happen, but more often it is quite the reverse—namely, that the reaction becomes more positive, an occurrence which is seen in the primary, secondary, and latent stages. The opposite also frequently occurs, *i.e.*, a patient with tertiary lesions giving a negative reaction, gives a positive reaction after an injection of salvarsan.

Case 7.—The patient contracted syphilis 25 years ago, for which he took mercury at irregular intervals for 4 years. For the past 5 years he had been troubled with cutaneous gummata, which disappeared under mercury and iodides, to reappear quickly after treatment was discontinued. In 1911 the patient had three intramuscular injections of salvarsan, and he came up for a Wassermann test just after Christmas of the same year. There were no symptoms at the time.

No. of injection, and result.		24 hours after.	48 hours after.	5th day.
1st injection	+++	+++	+++	+++
2nd injection (8th day after 1st)	+++	+++	+++	+++
3rd injection (8th day after 2nd)	+++	++	+++	+++
4th injection (8th day after 3rd)	++	+	+	+
5th injection (8th day after 4th)	–	–	–	–
6th injection (8th day after 5th)	–	–	–	–

Six months and a year later, although patient was under mercury, the Wassermann's reaction was positive.

Case 8.—A man, aged 42, contracted syphilis 18 years ago, for which he was treated with mercury (pills) internally for 3 years. A few years later he was much troubled with headaches, which were only relieved by mercury and iodides; and the moment treatment was stopped, the headaches commenced again. From time to time, the patient had cutaneous gummata and some soft nodes (gummatous pericranitis) on his skull. When he came up for advice he had a gumma over his frontal bone, and it had eroded a portion of the external table; headaches were bad, and the patient complained bitterly of losing his memory.

No. of injections, and result.		24 hours after.	48 hours after.	5th day.
1st injection	+++	−	−	+++
2nd injection (8th day after 1st)	+++	−		
3rd injection (28th day after 2nd)	+++	++	+++	+++
4th injection (8th day after 3rd)	+++	++	+++	+++
5th injection (8th day after 4th)	+++	+	++	+++
6th injection (8th day after 5th)	++	−	+	−
7th injection (8th day after 6th)	+++	−	++	+
8th injection (8th day after 7th)	++	−	+	−
9th injection (8th day after 8th)	+	+	−	

On testing the reaction on the 7th, 14th, 21st and 28th days after the last injection, it was found to be negative on each occasion and has remained negative for 2 years.

When approaching the end of treatment, and when all the reactions are negative, and in cases in which the amount of reagin is normally small—namely, cases of arteriosclerosis, cerebro-spinal syphilis, syphilitic epilepsy, and hemiplegia—each serum should be tested in gradient increasing strengths.

When a serum stronger than normal is used, controls should never be omitted, to show that it has no hæmolytic power on the sheep's blood corpuscles, an occurrence which is not at all uncommon, especially when the serum has been allowed to remain with its corpuscles for a few days. Therefore it is desirable to pipette off the serum as soon as possible after the blood has been withdrawn, and it is always better to inactivate the serum as soon as possible, since sera left at room temperature, or more especially in an ice incubator, soon acquire the property of fixing complement.

It sometimes happens that cases nearing the end of treatment, for instance, after the 4th or 5th injection, give a weak positive reaction only between the 3rd and 4th week, which becomes negative within a few hours of repeating the injection. Therefore, before a patient is finally discharged, a test should be carried out between the 21st and 28th day after the last injection. Such cases usually require only one more injection before the treatment with salvarsan is complete.

Patients who have had syphilis, and give a negative Wassermann's reaction, are either cured or in the latent stage; which of the two can only be ascertained by giving a provocative injection of salvarsan, and then testing the blood.

Case 9.—A man, aged 29, contracted syphilis 5 years ago. The attack was very mild, but nevertheless the patient continued his mercury treatment (pills and injections) for four years. A recurrence never appeared. On three different occasions the blood had given a negative Wassermann's reaction, but the patient being anxious to marry was desirous of an injection of "606" to make things sure.

No. of injection, and result.		24 hours after.	48 hours after.	5th day.	14th day.
1st injection	−	+	+++	−	
2nd injection (8th day after 1st)	−	+	+++	++	
3rd injection (8th day after 2nd)	−	+	+	++	
4th injection (8th day after 3rd)	+	+	+	+	+
5th injection (21st day after 4th)	+	−	−	−	
6th injection (8th day after 5th)	+−	−	−	−	
7th injection (8th day after 6th)	−	−	−		

The reaction was also negative on the 7th, 14th, 21st and 28th days after the last injection. Mercury was prescribed for a year, and up to the second year the reaction was negative every time it was tested.

If the previous treatment has been recent—that is, only a few months ago—the appearance of a positive reaction may be delayed, or, as happened in several cases, may be positive in the 48 hours blood, and negative again on the 5th or even the 3rd day, to become only definitely positive on each occasion after the 2nd injection. In a few cases the reaction was not positive at all, until after the 2nd injection—cases of arterial syphilis.

Not only is the reaction determined by the time of the previous treatment, but also largely by the quality of that treatment. If the treatment has been good, then the occurrence of a positive reaction may also be delayed, and only a few injections are required to produce a negative reaction.

Several of my patients, who had been treated with mercury for from three to four years, and who had given a negative Wassermann's reaction on several occasions, gave a positive one after a provocative injection of salvarsan, and required from four to six injections before a negative reaction was obtained. In my opinion prolonged administration of mercury has seldom cured a case of syphilis, it merely abolishes symptoms and drives the patient into the latent stage, from which he may on any future occasion return to the active; or, what still more often happens, insidious changes take place in his vessels, which cannot be detected clinically, until arteriosclerosis is well advanced, or serologically, because the amount of reagin circulating in the blood is too small to estimate. There is no doubt that in syphilis there is a strong tendency towards spontaneous cure, and possibly if every syphilitic patient lived long enough, provided in the meantime he had not succumbed to the disease, he would outlive it. Mercury does not directly cure syphilis, but it increases this tendency towards spontaneous cure.

In cases of cerebro-spinal meningitis, in which the cerebro-spinal fluid gives a positive Wassermann's reaction, repeated injections of salvarsan may convert the positive into a negative reaction, and at

the same time cause the lymphocytosis to disappear, but in the majority of cases the reactions become positive again, sooner or later. As the cerebro-spinal fluid is weak both in its reagin content and in complement-fixing capacity, it should invariably be tested in increasing strengths up to 1000 per cent.

In cerebro-spinal syphilis it is not at all uncommon to find that the Wassermann's reaction is negative in the blood, and positive in the cerebro-spinal fluid, becoming positive in the former only after treatment.

However many injections of salvarsan be given, it is always wise to supplement them with at least one year's treatment by mercurial injections and iodides. Even then one may not be successful in preventing a recurrence from appearing later, as no test exists which will prove the absence or presence of spores, and no treatment exists which will kill them directly.

If the above course is followed, experience has so far shown that a cure in the primary and secondary stages of syphilis is possible, but by no means certain. In the tertiary cases a cure is, for the most part, impossible. Therefore, in the early stages of syphilis, in my opinion, salvarsan can be used with the idea of curing the disease, and in some of the late stages of abolishing the symptoms only. There is no doubt that some patients who have shown tertiary symptoms become spontaneously cured; a cure in tabes can certainly occur.

Nearly every case which I have treated by several injections of salvarsan and one or more years' treatment with mercury has, up to the present, remained free of symptoms, and some have been under observation for three years from the time treatment was begun. A majority of the cases has, however, later given positive Wassermann reactions, and a peculiarity about most of them has been that the reaction appeared paradoxical, *i.e.*, one week or one month it was positive, while the next week or month it was negative again. The cause of this paradox is far from clear, but, nevertheless, its occurrence should be a stimulus to make us probe the rationale of the Wassermann's reaction down to the very bottom to see if we are justified in always regarding a positive reaction as necessarily indicative of active syphilis.

It is noteworthy that of two individuals, in exactly the same stage of disease, with the same lesions, one may give a negative reaction after four injections, while in the other, six or more may be required before a negative reaction is obtained. Again, a permanent negative reaction is most easily obtained when the treatment is continuous, that is when the injections of salvarsan follow closely upon one another, and when mercury is given afterwards for a year. For instance, early cases of syphilis, which had received one or two injections of salvarsan several months back, have required nearly the same number, given continuously, as presumably would have been required, had those previous injections not been given. Therefore it is important, if a course is going to be started, that it should be persevered with, until the desired effect is obtained.

The Luetin Test.

Several observers have attempted to obtain a substance which would give a reaction in syphilis, analogous to that obtained in tuberculosis by the intracutaneous injection of tuberculin (the v. Pirquet's reaction). This became possible when the *Spirochæta pallida* was cultured, and from such cultures Noguchi (6) prepared an extract to which he gave the name "luetin."

Noguchi distinguishes three reactions: (*a*) the papular; (*b*) the pustular; (*c*) the torpid. The papular form is most commonly seen in secondary syphilis; the pustular form is seen most often in tertiary and in congenital cases.

The torpid form is the rarest, and is recognised by the fact that the reaction does not appear until a few days after the test has been applied.

Noguchi found that in untreated cases, in both the primary and the secondary stages, the luetin reaction was usually negative, while in the latent stage, and in other stages in which treatment had been given, the reaction was generally positive.

In cases of tabes and general paralysis only 50 per cent. gave a positive reaction. Other American observers (7, 8, 9) who repeated Noguchi's work obtained similar results.

Noguchi very kindly sent me some material which I tried on several cases. At the same time as I was using luetin, I was also experimenting with the cutireaction obtained with various specimens of gonococcal vaccines (19).

In early cases of syphilis, as in acute cases of gonorrhœa, whether the gonococcus was limited to the urethra or had already become systemic, the cutireaction was generally negative.

In late cases of syphilis and in late cases of gonorrhœa, especially when there was a metastatic complication, the reaction was almost invariably positive, and often very markedly so. It not only varied in intensity, but also in the time which elapsed between giving the injection and the onset of the reaction. If a test for diagnosis is required at all, it is most necessary in the early stages of the disease, when cutireactions are usually negative; therefore, as a means of helping the practitioner to diagnose a sore, the luetin reaction cannot be said to have much value. With luetin, as with the gonococcal vaccines, the reaction depends not only upon the strain used, but largely upon the experience of the operator, as what is considered a positive reaction varies with almost every observer.

It is important to note that a positive cutireaction only signifies that the patient has had the disease, not necessarily that he has still got it.

Furthermore, the luetin cutireaction is not absolutely specific, as I have been able to get positive reactions in patients who have never had syphilis, 3 cases in 25 controls, and I have been able to produce a positive reaction in cases of syphilis with substances other than luetin, namely, with certain fatty acid adsorption complexes with globulin.

Boas and Ditlevsen (10) in a recent article also found that

positive reactions were to be obtained in non-syphilitic cases, as many as 15 in 124.

In latent and tertiary stages of syphilis, although the luetin reaction is not more often positive than the Wassermann's reaction, cases are to be met with in which the former is positive and the latter negative, and *vice versâ*. It has been suggested that in these two stages both tests should be applied, but this is unnecessary, as such cases are extremely rarely sources of infection; a clinical diagnosis is more valuable than both, and a positive reaction with either is no certain criterion that the disease is active, and therefore requires treatment.

A peculiar phenomenon has been noted by Müller and Stein and Klausner (14), that occasionally a case of tertiary syphilis, with a negative Wassermann's reaction and a positive cutireaction, gave a positive Wassermann's reaction after the cutaneous test had been applied.

Owing to the difficulty of manufacturing luetin, extracts of syphilitic organs have been prepared and used for the cutireaction.

One of the best tissue extracts is that prepared from the lungs of congenital syphilitic infants (pneumonia alba); it goes by the name of Pallidin, and can be obtained from the Firma Merck in Darmstadt.

Klausner did the experimental work in connection with this extract, and his results have been set out in a recent number of the "Münchener Medizinische Wochenscrift" (14), and they are shortly as follows:—

In 1,200 control cases the reaction was always negative. In early cases of syphilis the reaction was negative, but positive in the greater percentage of tertiary cases and congenital syphilis.

The results in the late cases compared favourably with the Wassermann's reaction. Oddly enough, the reaction was invariably negative in cases of tabes, G.P.I., and arterial syphilis.

So much more has yet to be learnt about cutireactions in general, that at present they have little or no practical value.

The Biology of Stages of Syphilis.

The enlargement of the lymphatic glands in syphilis bears no ratio to the severity of the disease, but is an index to the protective capacity of the host. In view of the protective action of the glands; their removal, which has lately been suggested as a means of treatment, would appear to be contra-indicated.

The statement that enlarged glands are an index of the protective mechanism of the host is supported by the fact that they are seldom enlarged when a chancre becomes phagedænic, since the secondary infection succeeds in annihilating the leucocytozoon.

The organisms spread along the lymphatics from the nearest chain of glands, until other chains are reached, and ultimately all the glands in the body are infected. While the lymphatic extension is proceeding, the organisms are also pervading the body by means of the blood-stream. In this way, the so-called secondary symptoms arise. The symptoms of invasion will eventually disappear without treatment, but the disappearance is hastened by the administration of

mercury, which works slowly, or by salvarsan, which works almost instantaneously. When the organisms have become diffused by the blood, the secondary stage is reached.

The action of treatment is to destroy primarily the spirochætæ, which are responsible for the symptoms. The other phases of the virus of syphilis, in my opinion, are destroyed secondarily and indirectly. As the spirochætæ are responsible for the lesions, the protective mechanism of the host will be especially directed against these bodies, but their death does not mean that the spores described by me are destroyed.

If no treatment is given, or if mercury alone is prescribed, the spirochætæ will vanish for a time, the spores, as they seek fresh hunting ground, will spread peripherally, so that when symptoms recur, the lesions will be in the form of circles or segments of circles.

If salvarsan be prescribed, the spirochætæ are destroyed at once; it may be assumed that the spores are temporarily crippled *in situ*, so that when they again start their life-cycle, this will occur in the same situation: hence recurrences after salvarsan simulate the lesions for which salvarsan was given.

The early lesions of syphilis are more infectious than the recurrent, therefore insufficient use of salvarsan, or failure to supplement its administration with mercury, may give the patient a false sense of security, so that there will be no apprehension of a recurrence, and it will not be recognised when it does appear, and no care will be taken.

Six cases have been seen by me, in which the wife was infected by her husband, who was told that he was cured after he had had two injections of salvarsan.

In view of what has been stated, one has felt justified in advising several injections of salvarsan, given at the shortest possible intervals, to be followed by at least one year's treatment with mercury.

The longer the spores are present in any one spot, the more chronic inflammatory changes will the local vessels exhibit. Hence, should a lesion occur, it will lead to still further trouble, to even obliterative endarteritis, which will result in necrosis of the skin over the area fed thereby, forming a gumma, and ushering in the tertiary stage of the disease.

A gumma occurs mechanically, the necrosis, in my view, not being due directly to the specific organisms. In a necrosis, saprophytic organisms flourish, which at once kill the leucocytozoon, with the result that its secretion is to all intents and purposes non-infectious. The specific organism has been found to live for a time in the tissue surrounding the necrosis.

The way in which the nervous system reacts to the cause of syphilis has always been more or less of a mystery, and even to-day the whole question is by no means solved.

It is certain that the nervous system, including in the system the blood-vessels and meninges, can be affected very early in the disease. In fact, it is highly probable that every syphilitic nerve lesion results from the direct presence of the organism, which reached the nervous system during the stage of the general infection.

The parts to be first attacked are the blood-vessels and the meninges, lesions of which clear up quickly under treatment. If the

infection of the meninges is very severe, the organisms spread peripherally, just as they do in the skin in cases showing severe secondary rashes. This means that some of the organisms get directly into the nerve substance. Such cases may end fatally in an incredibly short time, and one finds post-mortem acute perivascular inflammation, and hæmorrhages into the brain and spinal cord, and these hæmorrhages are much more marked in the former than the latter, especially in the pons. If the cerebro-spinal meningitis is not so acute, the patient recovers, and presents a picture of dementia præcox, as all the cases I have seen have been in young adults.

As in the skin, so in the nervous system there may be no early lesion, and the organisms may spread peripherally from certain spots, without giving rise to any visible signs, until, for reasons unknown, the cycle is again perpetuated; so that in the skin, for instance, the lesion resulting therefrom will be in the form of a circle or a segment of one.

The peripheral spread from any one spot appears to follow the lines of the blood-vessels, a point I have been able to prove in the following way :—

If a patient who has a primary sore on the tip of a long foreskin is circumcised, and sections are made of the base, it will be found that practically all the different bodies of the leucocytozoon are situated in the walls of the blood-vessels.

If the brain, from a case of G.P.I., is examined, provided the meninges still show signs of inflammation, vessels will be seen running into the brain substance from the pia mater, and it is mostly in the walls of these vessels that the phases of the leucocytozoon have been found. The main exception to the above rule is, that the *Spirochæta pallida* does not necessarily follow the route taken by the vessels; it may wander about and be found anywhere.

In probably the majority of the cases of syphilis, the organisms get into the meninges by means of the blood-vessels. They may give rise to no symptoms; their spread may not even be noticed, but, when they later give rise to symptoms, tabes or G.P.I. is the result.

In other words, tabes and G.P.I. arise from a direct spread of the organisms, on the one hand into the cord, and on the other hand into the brain.

My reasons for thinking that these two so-called parasyphilitic affections arise by a direct extension of the organisms from the meninges are the following :—

The meninges of the brain are most closely attached to the brain substance over the cortex, and the blood-vessels run directly from the meninges into the nerve tissue. In all cases of G.P.I., the morbid changes are practically limited to the cortex, and the earlier the case, the nearer to the surface are the histological changes to be found; while, in late cases, only the superficial part of the cortex may show the results of inflammation, the recent areas being deeply situated.

In the case of the cord, the blood-vessels run from the meninges along the septum posticum, into the posterior columns. The posterior part of the cord has a better blood supply than the anterior part. Hence, late lesions of the cord are usually tabetic.

Early syphilitic lesions of the cord usually affect the anterior part and the myelitis which results is, in my opinion, an endarteritic

lesion, analogous to that of the brain which causes hemiplegia—which is also a frequent early symptom of syphilis.

The anterior surface of the cord corresponds to the base of the brain; the blood supply to both comes from the same source. There is no anterior meningeal ligament along which organisms can spread, the main blood-vessel is free; therefore, one might imagine a lesion of the anterior part of the cord to be of the nature of an endarteritis.

The early endarteritic lesions of syphilis are peculiarly localised, and they are due to the direct local action of the organism, which starts its life-cycle in the coats of the vessel, a point I have been able to demonstrate. As the cycle may start in one part, and not necessarily in the whole circumference of the vessel, the unipolar changes to be met with are accounted for. In time the organism may spread, and, if it did so in the anterior part of the cord, it would immediately cause nerve degeneration. This is probably the pathology of those late anterior horn lesions, which are occasionally to be met with in syphilis.

Lateral column lesions are also to be met with, although very rarely, in spite of the close connection this part of the cord has with the meninges, through the ligamenta denticulata; the reason is that there is no direct blood supply between the two at this point.

To sum up, the lesions of the brain and the cord are analogous. The early lesion of the brain is an anterior one—hemiplegia, which corresponds with an anterior lesion of the cord—myelitis. The late lesion of the brain is a posterior one—G.P.I., which corresponds to a posterior lesion of the cord—tabes. An analogy also exists between these nerve lesions and the skin lesions. The early nerve lesions are vascular, so are the early lesions of the skin, and both are localised.

The late nerve lesions correspond to the recurrent serpiginous syphilides. Finally, a gumma may occur as a nerve and as a cutaneous lesion.

Direct extension of the organisms into the central nervous system, by way of the peripheral nerve trunks, must not be lost sight of, but, except in the case of the cranial nerves, perhaps this mode of spread in syphilis is unlikely, for the simple reason that lesions of nerves along which the organisms have spread give rise to symptoms early in the disease. Moreover, peripheral syphilitic nerve lesions affect both motor and sensory nerves. Finally, a posterior column lesion frequently exists, without a corresponding lesion in the posterior root ganglion.

One of the chief reasons observers give to explain the occurrence of tabes, from a spread of the organisms along the posterior root sheaths, is that the *Spirochæta pallida* has been found in sections of a chancre in the nerves of the skin. In my opinion, such an occurrence is a coincidence, since the *Spirochæta pallida*, owing to its motility, can be found in any tissue. Furthermore, since the *Spirochæta pallida* is not the cause of syphilis, its extension along the lymphatic sheaths of the posterior root nerves would not give rise to tabes. For symptoms of syphilis to occur, the whole of the life-cycle of the protozoon must take place *in loco*, therefore the spores and the other phases must be present in the brain and spinal cord, in cases of G.P.I. and tabes. I have examined brains from

ten cases of G.P.I., and in nine of them I have found the phases of the leucocytozoon, which mostly occurred in the walls of the blood-vessels, while the *Spirochæta pallida* had no particular distribution. The case in which I failed to find the bodies was an old case of G.P.I., which recurred and died quite suddenly. During his last illness the patient had pneumonia, and it was not certain whether the death was due to the lung trouble or to the brain trouble. It is highly probable that the toxin of the pneumococcus was responsible for the so-called recurrence of the G.P.I.—a view which is favoured by the fact that no recent inflammatory changes were to be found in the cerebral cortex.

It is possible that the spore travels along the posterior nerve roots, and so causes tabes; but since I have so frequently been able to find the spore and the other phases in the walls of blood-vessels, since an analogy doubtless exists between tabes and G.P.I., and since I have been able to find the phases in the walls of the blood-vessels in the latter condition, it is more than likely that my view of the pathology of tabes is the correct one.

Supposing for a moment that spores did travel along the posterior nerve roots and obtain entrance into the nerve tissue of the posterior columns, how are they to develop?

Spores can only develop in connective tissue cells, which do not occur in nerve tissue, except in the walls of blood-vessels, therefore it is only reasonable to suppose that late nerve lesions result from a direct spread of the organisms from the meninges in the walls of the blood-vessels. Finally, I have frequently found the phases of the leucocytozoon in the pia mater in cases of G.P.I.

For convenience in dealing with lesions of the central nervous system, the body will be considered as consisting of two divisions: (*a*) that part which is bathed by blood, *i.e.*, the systemic division; (*b*) that part which is bathed by cerebro-spinal fluid, *i.e.*, the nervous division.

The distinction is necessary, since there is practically no connection between the blood and the cerebro-spinal fluid, so that sterilisation of the former may still leave the latter affected. Complete sterilisation of the body will naturally include both the systemic and nervous parts. This point is illustrated by the following case:—

Case 10.—A patient, a boy aged 17, contracted syphilis in October, and came under care the following January, being covered from head to foot with a diffuse papulo-erythematous eruption. After eight weekly intravenous injections of neo-salvarsan, the Wassermann's reaction became negative, then mercurial injections were carried on until April. Three weeks after treatment was stopped, the patient began to complain of headache, insomnia, and loss of appetite. These symptoms became gradually worse, and he came up for advice again in June, by which time he had lost two stones and a half in weight. The boy looked pale and emaciated, the pupils were slightly unequal, and the reflexes were on the plus side, and there was a general hyperæsthesia, otherwise nothing abnormal was discovered—Wassermann's reaction was negative. Fearing cerebro-spinal syphilis, a lumbar puncture was performed with the following extraordinary result:—

Cells: 450 per cubic centimetre; 68 per cent. lymphocytes; 27 per cent. endothelial cells; 5 per cent. polymorphonuclears.
Nonne Apelt reaction positive. (This reaction invokes the presence of globulin.)
Wassermann's reaction positive in all dilutions, *i.e.*, from 10 per cent. to 500 per cent.

The early onset of cerebro-spinal syphilis makes this case interesting, since few books point out that cerebro-spinal syphilis may occur a few months after infection. I have seen four cases, one of which developed nervous symptoms 4 months after the chancre was first noticed, no treatment having been received. The other three cases I took to be cured by salvarsan and mercury.

The suggestion at once offers itself that sterilisation of the blood may hasten an attack of cerebro-spinal syphilis owing to a diminution of antibodies.

This is, however, far from being the chief point to be learned from such cases. The nervous part of the body can be reached by the infective agent as easily as the systemic, and symptoms of an affection of the former may occur, in spite of treatment.

The former point is still further emphasized, by the fact that the examination of the cerebro-spinal fluid of several early cases of syphilis showed pathological changes. The cerebro-spinal fluid of latent cases was also examined, and that from cases which had been well treated, and in whom the Wassermann's reaction in the blood was negative, pathological changes were found, although no suggestion of disease manifested itself clinically, an occurrence which is brought out in the following case:—

Case 11.—A patient contracted syphilis 8 years ago, was treated with mercury in the ordinary way for 3 years, and developed no symptoms later. Wassermann's reaction in blood negative, but it became positive after a provocative injection of neo-salvarsan.

Cerebro-spinal fluid:—
Cells: 25 per cubic centimetre.
Nonne Apelt: negative.
Wassermann's reaction: double quantity of serum undiluted +++, *i.e.*, 200 per cent.
Serum undiluted +, *i.e.*, 100 per cent.
Serum 1 in 5 —.
Serum 1 in 10 —.

It would seem that cerebro-spinal syphilis, tabes, and G.P.I. are born when the syphilis first appears, but remain dormant for a varying period, depending perhaps upon the quantity and quality of the antibodies in the system, only to appear as symptoms late in the course of the disease.

Whether or not these surmises are correct, it behoves every patient to seek advice on the appearance of a sore, to have it diagnosed without delay, and to receive sufficient treatment to sterilise the whole system.

It further increases the necessity for a more frequent examination

of the cerebro-spinal fluid; but, alas! even with the knowledge that there is mischief lurking there, it is at present possible only to keep it at bay.

It is very seldom that treatment given by the skin, muscle, or vein can effect a complete cure in a case of cerebro-spinal syphilis, tabes, or G.P.I., owing to the fact that the diseased area does not receive a sufficient dose of the drug prescribed. Homer Swift and Ellis (15) have obtained good results by injecting, intraspinously, serum rich in antibody; but it is feared the treatment is only palliative, and several injections are necessary to obtain a satisfactory result. Moreover, there are few people who would submit to repeated lumbar punctures.

Clinically, we draw a very sharp line between cerebro-spinal syphilis, tabes, and G.P.I. So sharp is it that we fail to see the common foundation upon which the three are built. The three conditions are extremely closely related, and which one is going to crop up will depend largely upon the treatment that has gone before.

If sufficient salvarsan to cure the symptoms be given to a patient during the stage of general infection, but not to sterilise the system, and if a recurrence appear, it may be generalised and indistinguishable from the original trouble. The action of the drug is sudden; on the basis of the life-cycle, as described by me, it may be considered that the gametes which are responsible for the symptoms are killed; the body has no further need to form antibodies, and all is well. The spores remain *in situ* and, having no antibodies to disturb them, can resume their cycle and give rise to new gametes in exactly the same spots as those in which they were stunned.

Under the influence of mercury—the action of which is insidious, and not powerful enough to destroy the gametes as previously described, or to give the host its stimulus for the formation of antibodies—the spores, to some extent, become crippled, extend peripherally to find fresh hunting-ground, and, if they subsequently multiply, they can give rise to a sufficient number of gametes. The lesions will be fewer, more localised, and in the form of circles or segments of circles. Later, owing to the presence of the spores, the vessels become inflamed. This leads to narrowing of the lumen, diminution of blood supply to part, consequent necrosis, and so a gumma.

During the stage of general infection, the nervous system is not spared, and that part of it which is fed by blood, namely, the meninges and blood-vessels, becomes infested with organisms. Sterilisation of the systemic part does not sterilise the meninges, as shown by the case (Case 10) to which I have just referred. There are no antibodies except in the cerebro-spinal fluid—a fact which would appear to be for the benefit of the nerve tissue rather than for the meninges—with the result that a generalised meningitis ensues. The cases of cerebro-spinal syphilis seem to me to be relatively increasing. This, if a fact, is explained on the hypothesis that, owing to the feebler action of the antibodies in the cerebro-spinal fluid, compared with that of those in the blood, there is nothing to prevent the extension of the parasites from the meninges into the nerve tissue; and this is more likely to occur where they come most closely in contact, viz., brain and cord.

The former results in G.P.I., the latter in tabes. Most of the

blood-vessels extend into the cord from the meninges along the septum posticum, with the result that the posterior part of the cord is better supplied with blood than the anterior part, and, as the syphilitic organisms extend along the paths of the vessels, it becomes clear how tabes arises.

The vessels to the anterior part of the cord do not run along any septum, and therefore have no close connection with the meninges.

A syphilitic lesion of the anterior part of the cord is a vascular one, and is analogous to the early endarteritis of the basilar artery and its branches in the cranium. This makes transverse myelitis and early syphilitic hemiplegia similar pathological conditions.

General paralysis is brought about by a spread of the organisms from the meninges into the cortex of the brain, which brings it into the same pathological condition as tabes. Pure endarteritic lesions, if treated early, are cured, the patient recovers without a trace of what has happened, and the condition does not tend to recur.

Pure nerve lesions, such as tabes and general paralysis, are not cured.

Should the organisms spread in the nervous part, but be crippled in the way described in the systemic part, as occurs under treatment by mercury, localised symptoms prevail; the cerebro-spinal syphilis will become divided, with the appearance of two separate types, *i.e.*, the pure cerebral type and the pure spinal type.

Further, when the extension of the organisms has become greater and the vascular disturbance more marked, tabes and G.P.I. will follow, and when they appear will depend upon the period in the course of the disease in which the production of the systemic antibodies is checked. I have known cases of syphilis in which the Wassermann's reaction was negative develop tabes and G.P.I., and it was only when the symptoms of these two conditions became manifest that the blood gave a positive reaction.

If adequate treatment is begun before the nervous system is attacked, it will presumably always remain free. If treatment is begun after the nervous system has been attacked and the treatment is sufficiently early in the disease to stop the host producing antibodies, symptoms of the nervous system, should they arise, will be those of cerebro-spinal meningitis. If the production of antibodies be not stopped till late in the disease, tabes and G.P.I. will ensue. Therefore, starting treatment in the secondary stage with mercury alone, or with one or two injections of salvarsan, the patient will run greater risks of getting tabes and G.P.I. If, on the other hand, several injections of salvarsan be given and supplemented with mercury, cerebro-spinal syphilis is more likely to result. Cerebro-spinal syphilis is preferable to so-called parasyphilis, but the absence of both would be better still, and that can only be guaranteed if the patient is put under treatment before the nervous system is attacked, since, although the pathological changes in the cerebro-spinal fluid may be made to disappear by treatment, sooner or later they all come back again.

The moral of all this is, to diagnose a sore at once, and to put the patient under the most adequate treatment possible, or, in other words, treatment which will suffice to cure the disease completely.

Syphilis in Women.

This part of the subject requires a special heading, since the disease, as it affects pregnant women, is altered in such a way that it cannot easily be recognised, and also because the offspring may be infected.

Syphilis in women may be looked upon as the greatest curse of the disease, since a woman who has once conceived a syphilitic infant may infect *in utero* all her subsequent offspring, although the father of the latter may be a different husband, who has never had the disease.

To make matters worse, conceptional syphilis is not recognised until the infant has been seen to settle the diagnosis, owing to the fact that many mothers show no evidence of the disease until after the child-bearing period is over.

The following two cases which I showed before the Dermatological Section of the Royal Society of Medicine, April 21st, 1910 (16), will serve to illustrate the point:—

Case 12.—Mrs. A. B., aged 46 years, came up to St. Bartholomew's Hospital complaining of a rash on her right arm. The rash had appeared about Christmas 1909, and, some short time before, she had had some sore places on the right leg. The lesion on the arm was a gumma, and the right leg was covered with the scars of gummatous ulceration. This patient was 21 years old when she married, and neither before her marriage nor since, until the date above mentioned, had she ever experienced the slightest evidence of syphilis. She had had four miscarriages; eleven children were born, two of whom were still living—the results of the second and fourth pregnancies. All the other children had died within six months after birth as the result of syphilis. Her last pregnancy had been a miscarriage, immediately after which her leg became bad; this period also corresponded to the change of life. The patient had given a strong positive Wassermann's reaction. Her second pregnancy resulted in the birth of a son, who had given a negative Wassermann's reaction, as had also his wife and child. The fourth pregnancy resulted in the birth of a daughter, who had also given a negative Wassermann's reaction. Neither child had shown the least taint of the disease.

Case 13.—L. B., aged 47 years, had come up to the West London Hospital complaining of sores on the calf of the right leg, which were typical gummata. As in the preceding case, the ulcers had appeared just after the "change of life." The patient had been pregnant nine times; the children had mostly been premature. Some had been born alive, others born dead, but not one had lived for more than three weeks.

Since 1910, I have seen numerous similar cases, in all of whom I was able to obtain a positive Wassermann's reaction, provided the child-bearing period was over. This led me to rely upon, and to do the test, in every case in which a syphilitic infant had been born, when, to my surprise, I found that many cases of women

who were giving birth to syphilitic children themselves gave a negative Wassermann's reaction.

A general rule can be formulated, viz., that if a woman contracts syphilis after she has conceived, the Wassermann's reaction will be positive, because the disease becomes generalised, and behaves in the ordinary way; that if a woman contracts syphilis at the time of conception, the Wassermann's reaction will often, if not always, be negative, because the disease does not become generalised, at any rate, not until some later date.

Herein we have the explanation why such patients only develop manifestations after the child-bearing period is over, and why it so frequently happens that the first and last pregnancies result disastrously, while one or more healthy children may be born in the middle. It is interesting to inquire into the rationale of conceptional syphilis.

The germ must, in the first instance, be conveyed by the semen. But does the germ, which travels with the embryo along the Fallopian tube into the uterus, develop after a time into the gamete forms described by me, which I regard as responsible for the symptoms, at the expense of the embryo—with, maybe, its death—leave some of the sporozoites behind after its expulsion, to be already there to develop at the expense of the next embryo? Or, does the mother get infected directly, but the symptoms are prevented from recurring, owing to the formation of some chemical substance, possibly in the form of a lipoid from the embryo, which prevents the gametes from being developed?

When the question was discussed after the *Spirochæta pallida* had been discovered, when the *Spirochæta pallida* was held to be responsible for everything syphilitic, only confusion resulted. If my discovery of the *Leucocytozoon syphilidis* is accepted, and the views accepted that the sporozoite is the infective agent, and that the gametes are responsible for the symptoms, "either—or" need not appear in the above illustration, as both in part may turn out to be correct.

It may be considered that the sporozoites, themselves potentially harmless, travel in the semen, reach the uterus with the embryo along the Fallopian tube, and find themselves in both the maternal and fœtal portions of the embryo. Those in the fœtal portion, after a period of some weeks, develop into gametes, which may or may not kill the embryo.

Those in the maternal portion find themselves unable to develop owing to a chemical substance, from the chorionic cells, which circulates in the mother's blood, but not in the fœtal, and so they remain dormant for a time. Herein lies the solution of the phenomenon that a mother may give birth to a severe syphilitic infant, without herself even giving so much as a positive Wassermann's reaction.

The theory above put forward will also explain the reason why a woman who has once given birth to a syphilitic child is always liable to do so again, although the father of her later children may be another husband, who has himself never suffered from the disease.

Hence the necessity for treating such a case throughout the whole period of each succeeding pregnancy.

There is no necessity to refer to the lengthy discussion relating to the greater frequency of maternal over paternal infection, or *vice versa*.

A father may be the cause of his first infant contracting the disease; the mother, *ipso facto*, becomes likewise affected; her future children may be by another and a healthy man, but they may all be syphilitics. Therefore, maternal syphilis must obviously be more important and frequent than paternal syphilis.

The only reliable information as to the national loss by ante-natal syphilis is the oft-culled figures of Hochsinger (11, 12).

This observer, since 1869, had been able to keep under observation 134 women who showed no signs of syphilis, but had given birth to syphilitic children. These women had given birth 569 times, 253 of the children being born dead, *i.e.*, 44·4 per cent; 263 were syphilitic, and 53 were without a taint. Of the 263, 55 died before the fourth year, *i.e.*, over 20 per cent.

These figures are so appalling that it is of the utmost importance for the State to have particular regard for the welfare of syphilitic women, in seeing that they are properly treated. The question may very naturally be asked, what evidence is there to show, supposing infected mothers are treated throughout each and every pregnancy, that births of healthy children will result? Statistical evidence there is none, so reliance must be placed upon the impression observers have received from their clinical experience. In my private practice, I have done my utmost thoroughly to treat throughout each and every pregnancy of every pregnant woman, with the result that I have never failed to see not only a child born, but none that gave a positive Wassermann's reaction. Owing to the fact that the mother is seldom cured by such treatment, it must never fail to be repeated, and it is never safe for her to suckle her child, as the infective agent can pass in the milk.

Treatment by Salvarsan.

In discussing the action of salvarsan reference will be made to the preparation which is now supplied, since it is considerably feebler in its action than the drug which was first used.

The majority of the cases of primary syphilis to which one injection was given over three years ago are now both clinically and serologically sound.

The majority of the cases of primary syphilis to which two injections of salvarsan were given when the drug came upon the market have developed symptoms since. Of those which were already in the stage of general infection nearly all showed recurrences within a year, and many within 3 months.

It is only since the rule has been followed to give as many injections as are necessary to procure a negative Wassermann's reaction in the blood, taken between the 17th and 48th hour after the last injection, and to prescribe a year's treatment with mercury, that the fewest recurrences have been observed. Probably, in a few more years, many of those which have not so far recurred, will develop symptoms, but until our knowledge increases this procedure is the best.

In the primary stage, provided sufficient injections of "606" are given to procure a negative Wassermann's reaction in the blood withdrawn within the limits above specified, and that the treatment

is further augmented by 24 intra-muscular injections of mercury, given in three courses of eight weekly within the 12 months, in the light of our present knowledge a cure is possible. In the secondary stage a cure may possibly be obtained.

Success for the same treatment in the latent stage of the disease and in the stage of early recurrences is improbable, while in the stage of late recurrences, gummata, nervous syphilis, etc., a cure is impossible, *i.e.*, broadly speaking, since spontaneous cure in any stage is possible.

In the primary stage three to five injections, and in the secondary stage six to nine injections are required. In late cases even 15 or more injections of salvarsan may fail to procure a negative Wassermann's reaction, and, supposing a negative Wassermann's reaction be obtained, it is not long before it becomes positive again.

In late cases it appears wiser to give two or three injections of "606" to heal the symptoms, and to augment it with a course or two of mercury and iodides, meanwhile informing the patient that he should place himself under treatment again the moment symptoms reappear. Such a patient may go years without a recurrence and, should symptoms reappear, they will almost certainly do so in the site of the previous recurrence.

It is universally agreed that the best way to give "606" is intravenously, and that the requisite number of injections should follow upon one another at intervals of not longer than 8 days. It has been frequently noticed that those cases which recurred to which only two injections had been given, with or without supplemental mercurial treatment, were never cured, if the subsequent treatment with salvarsan was given in injections of two.

I had two early cases of syphilis in which each patient received in all over 16 injections of salvarsan, given in pairs and threes with a course of mercury after each, who, after an interval of 3 months or more, according to the time at which the symptoms reappeared, were in much the same condition in the end as they were before treatment was started—a point in favour of the view that the spasmodic administration of salvarsan greatly lessens its therapeutic action.

A most important point to remember in salvarsan treatment is that if too few injections are given to a patient with infectious symptoms, should the symptoms recur, they will simulate those for which the drug was prescribed.

Several cases have been seen of patients who had condylomata, for instance, which disappeared under two injections of salvarsan, returning within 3 months with condylomata again, in spite of the fact that mercury was given as well.

After insufficient salvarsan treatment symptoms recur before the mercury which has been prescribed afterwards, usually in the form of pills, has had time to exert its action.

Insufficient salvarsan treatment, in the early stages of syphilis, will do more harm than good, as it gives the patient a false sense of security, and renders him for a longer period a danger to the community.

I have seen six cases, within the last year, of patients who had had two injections of salvarsan, infecting others, when they themselves

thought and had been told that they were cured. The cases which recur after several injections of salvarsan and mercury have been given, may be roughly divided into two classes: (*a*) Those in which symptoms reappear; (*b*) those in which the Wassermann's reaction becomes positive. Oddly enough, the majority of the former give a negative Wassermann's reaction, and the majority of the latter show no symptoms.

The interpretation of this paradox is at present not quite clear, but nevertheless the observation is an important one, since the class which cannot be recognised by a laboratory test is dangerous, for the symptoms are usually infectious.

Another interesting point is, that several of the cases which give a positive Wassermann's reaction, but exhibit no symptoms, give a negative Wassermann's reaction a few months later, and still show no symptoms.

As to whether salvarsan is more potent than neo-salvarsan or *vice versâ* different opinions prevail. I have given over 2,000 injections of salvarsan and over 4,000 injections of neo-salvarsan, controlling both by the Wassermann's reaction, and have come to the conclusion that the action of both is very much the same. Neo-salvarsan has the advantage of being less toxic and more easily administered than salvarsan, and it is perfectly safe to give it to out-patients.

The Action of Drugs, etc.

The body protection against syphilis is explained by me as follows:—

The cell which the host elaborates to protect itself from the syphilitic organism is the plasma cell. This cell is also called forth in any chronic inflammation. In all instances, the plasma cell is morphologically the same, but although its gross action may be similar in every instance, it is, nevertheless, specific in each case.

Take, for example, three plasmomata, one caused by syphilis, another by tuberculosis, and the third by a foreign body. Give an injection of salvarsan to patients suffering from these three conditions, and then make sections of all three lesions again. On examination, it will be found that only the plasma cells in the case of syphilis have altered.

To explain this specificity, we must probe the chemistry and physico-chemistry of the plasma cell.

This may be best done by calling attention to what has been described by me as the "oxygen chain" (17). Each link of this chain will be made up of free oxygen and a ferment, which activates it in varying degrees, according as to whether the first or last link of the chain is being dealt with. The first link is the red blood corpuscle, which contains free oxygen and a peroxydase: the ferment action is further increased by the iron in the hæmoglobin.

Oxidising enzymes have their action increased by metals; attention need only be drawn to the extraordinary accelerating action manganese has upon some plant oxydases in support of this statement.

Red blood corpuscles supply every tissue with oxygen in an active state.

The next link in the chain is a mast cell, one of the functions of which is to supply the basal cell layer of the epidermis with the active oxygen for the tyrosine-tyrosinase reaction, which results in the production of pigment, and this is one of the protective mechanisms of the body.

In support of this statement, reference need only be made to the well recognised increase of mast cells in urticaria pigmentosa, ephelides, and all known pigmentary affections of the skin. Another function is possibly to supply the next link with free active oxygen, namely, the nuclei of the cells of inflammation.

The accelerating element in the mast cell is possibly sulphur. Nuclei contain free oxygen and a ferment for activating the same, which is not nearly so strong as the peroxydase in the first two links.

Iron is the accelerator of the enzyme action in the nuclear link. The oxygen in the nucleus is used by the protoplasm of the cell and the nucleolus.

The last link in the chain is the protoplasmic, which contains oxygen, but no peroxydase. The activator probably comes directly from the nucleus, and indirectly from other cells which contain peroxydases, through the blood serum.

The accelerator of the enzyme action is the element contained in the drug which is prescribed against the infection; in the case of syphilis, arsenic, antimony, and mercury for instance. The lesions of syphilis may vanish without treatment, because of the ferment action of the serum and of the protoplasm of the plasma cells.

The protoplasm of plasma cells is rich in lipoid-globulin, and it is well known that lipoids are activators as well as carriers of ferments; therefore, in the protoplasm of plasma cells and in the serum the host has the means of overcoming the parasite. Treatment assists the host's resistance by accelerating the ferments, and therefore destroys the parasites indirectly.

What the ferment is, which destroys the leucocytozoon, is not absolutely proved, since I have only been able to arrive at the probable ferment by excluding others.

The syphilitic parasite appears to be shown, in my investigations, to be made up of a lecithin-globulin envelope which encases nuclein; therefore, it may be *à priori* thought that the ferment is either a lecithase or a protease.

A lecithase exists in normal serum which makes testing for a specific one difficult, but as a result of several experiments which I have undertaken with the serum, and more especially with the cerebro-spinal fluid, which, under ordinary circumstances, contains no lecithase, I have been unable to prove the presence of either a specific lecithase or a specific esterase. That is to say, the cerebro-spinal fluid in cases of G.P.I. and tabes did not break down lecithin, lecithin-globulin, triolein, tristearin, or a mixture of the fatty acid esters with lecithin-globulin.

The failure of Abderhalden's test, as used in pregnancy, to react with any regularity points against there being a specific protease.

In support of the ferment being an oxydase I have been able to collate the following facts:—

1. The granules in the epithelial cells of the choroid plexus give marked oxydase reactions, and as shown by Pighini (18) they are able to synthesise indophenol from a mixture of α-naphthol and dimethylphenylenediamine hydrochloride, the blue colour resulting being dependent upon an oxydase zymotic action.

2. These granules are increased in cases of G.P.I., which shows that the zymotic action is increased.

3. The cerebro-spinal fluid obtains its active properties from the cells of the choroid plexus.

4. I have been able to prove that the cerebro-spinal fluid from cases of G.P.I. is extraordinarily rich in oxydase ferments, while normal cerebro-spinal fluid contains none.

5. The cerebro-spinal fluids from cases of G.P.I. and cerebro-spinal syphilis, stain pure Nile-blue sulphate pink. This change from blue to pink is caused by glycerin esters and cholesterin esters and fatty acids.

6. The cerebro-spinal fluid in cases of syphilis of the central nervous system contains an excess of globulin.

7. This globulin is in an adsorption complex with lipoids.

8. Oxydases are frequently carried by lipoids; therefore, not only is there proof that the cerebro-spinal fluid from cases of syphilis of the central nervous system contains oxydase ferments, but also that the ferments are carried, and possibly accelerated, by the lipoid-protein complexes.

This view is still further supported by the analogy to the blood serum and plasma cells.

Still more convincing is the fact that I have been able to prove, that the granules of the epithelial cells of the choroid plexus, and the tigroid or Nissl's granules to be found in the nerve cells, consist of a lipoid-protein, and behave to reagents (3) similarly to the envelope of nucleoli, the protoplasm of plasma cells and the envelope of the syphilitic organism.

Pighini (18) showed that Nissl's granules also synthesised indophenol, especially those around the nucleus, which was to be expected, since the nucleus contains free oxygen and an oxidising ferment.

The explanation of the protective mechanism of the serum and the cerebro-spinal fluid against the syphilitic parasite, by means of oxidising ferments, is simple; in fact, it is its simplicity which makes one think that it is correct, for the more one considers how the body protects itself, the more convinced one becomes that it is not nearly so elaborate a process as all have been led to believe.

After all, why should such an exceedingly complex ferment as a lecithase or protease be manufactured specifically against syphilis? Supposing another protozoal disease sprang up in our midst to-morrow, the body would be ready to protect itself, and it could not possibly, in the short time at its disposal, manufacture highly complex specific ferments.

A most interesting point now crops up, namely, why are the spirochætæ destroyed more quickly than the other phases, and so quickly by salvarsan?

Chemistry showed that the male gamete or *Spirochæta pallida* had the strongest reducing action of all the phases. In *in vivo* staining,

it showed a marked affinity for methylene red, and it increased the reducing action of the female cell after impregnation.

In this reducing action, in my view, lies the solution of the problem as to why the male cell, and not the other cells, stains with silver nitrate in Levaditi's method of staining, and as to why the action of salvarsan is more marked upon the male cell.

The reducing action is due to an unsaturated fatty acid—a substance in which the male cell is especially rich, for two reasons: (*a*) because it is the result of an intracellular development; (*b*) because it has a very important function to perform, namely, that of impregnation. In other phases where combustion is less active, and the cells are more or less in resting forms, the fatty acids are more likely to be saturated than unsaturated.

The more unsaturated a fatty acid is in a complex, the more free OH- or hydroxyl-groups will there be.

To these free OH-groups different chemical substances can become attached; therefore, the *Spirochæta pallida*, owing to the fact that it contains more free OH-groups, can have its lipoid envelope altered by substances which combine immediately therewith.

In staining tissue with silver nitrate, in order to get a black colour, two things are necessary: one is that the silver must be taken up; the other is that it must be reduced *in situ*. Owing to the free OH-groups in the lipoid envelope of the *Spirochæta pallida*, the silver is readily taken up and reduced by the pyrogallic acid. In the other phases, on the other hand, there are no free OH-groups to take up the silver, so they therefore cannot stain black. The action of salvarsan is also probably to be explained in this way.

The arsenic fixes on to the free OH-groups, and robs the colloidal membrane of oxygen, hence the death of the organism. As there are no free OH-groups in the other phases, salvarsan cannot touch them. The destruction of the other phases is brought about by the ferment action of the protoplasm of plasma cells. Therefore, the action of salvarsan upon the spirochætæ is a direct one, and upon the other phases an indirect one.

From all that has gone before, it will be at once understood why syphilis is so hard to cure, for the simple reason that the spore contains little or no lecithin-globulin, and therefore, as a spore, it is potentially harmless, and so is not touched immediately by the host's ferments. In course of time, however, the spores are vanquished, owing to the continued oxidising efforts of the host, and this supports the statement that has more than once been made, namely, that, broadly speaking, syphilis is cured not by the treatment given, but by the resistance and protective machine of the host, which is assisted by treatment.

Finally, why is the nervous system attacked in the peculiar way it is?

Nerve cells are influenced only by the spirochætæ. Now, the spirochætæ, as may be remembered, are rich in unsaturated fatty acids, or, in other words, consist of a lipoid-protein coat which is unsaturated, and which will therefore, snatch up anything that comes in its way. It will snatch up fats, carbohydrates, and proteins.

Fats, and possibly carbohydrates, as such and in the form of

galactosides, are important chemical constituents of nerve cells. Therefore their abstraction will lead to nerve degeneration. In the same way, nerve cells can take up substances, and enable them to become part and parcel of their highly complex lipoids—amongst others, metals. Therefore, it is at once clear why arsenic in the form of salvarsan, when injected into the theca, causes nerve degeneration.

J. E. R. McDonagh.

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